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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/285,531	04/02/99	CHERNAJOVSKY	Y KIR95-01A

EXAMINER

HM12/0327

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LEXINGTON MA 02173-4799

ART UNIT	PAPER NUMBER
1646 FITZGERALD, D	8

DATE MAILED: 03/27/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE (3) month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-3, 6, 8, 13-17, 19-26 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-3, 6, 8, 13, 15-17, 19-26 is/are rejected.
☑ Claim(s) 14 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

~~☑ Notice of Reference Cited, PTO-892~~
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

D NOTICE ... re sequences with "Error Summary"

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1. Receipt of the preliminary amendment filed concurrently with the present application is acknowledged.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 for the reason(s) set forth on the attached "Notice to Comply . . ." and "Raw Sequence Listing Error Summary."

Applicant is requested to return a copy of the attached Notice to Comply with the response to this action.

3. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 6, 8, 15-17, and 19-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallach *et al.*, U.S. Patent No. 5,478,925.

Wallach describes and claims multimers of TNFR moieties, each such moiety corresponding to a soluble TNFR polypeptide (abstract), *e.g.*, the extracellular domains of the p55 and p75 human TNFRs (see col. 1 generally). It teaches that because both TNF and its receptors function *in vivo* as trimers, the multimeric receptors will be more effective than monomeric soluble receptors in binding to and inhibiting TNF (col. 3, lines 10-38). It teaches that dimers or trimers of the TNFR moieties may be advantageously made (claims 2, 3). It teaches that the monomers should be separated by linker moieties of "optimum length . . . to produce multimers which best bind TNF" and that "[t]hose of ordinary skill in the art will be able to determine" such optimum length. It notes that "the nature of the amino acids which link the monomers in the recombinantly produced multimer is not critical." Wallach also teaches that the multimers may be conveniently made as contiguous fusion proteins by recombinant methods (col. 4, lines 14-34 and Example 4), incorporating signal sequences as appropriate to the host cell system employed

(paragraph bridging cols. 12-13). It teaches that the multimers are suitable for the treatment of various TNF-mediated diseases and disorders, including septic shock, cachexia, GVHD, and various autoimmune diseases including rheumatoid arthritis (col. 4, lines 42-55). Wallach does not exemplify the preparation of any particular fusion multimer, nor does it specify the amino acid sequences of the TNFR monomers or the linker peptides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches that it is advantageous to do so. In the course of making such fusions, it would have been obvious to construct DNA encoding the fusion polypeptide by excising the TNFR sequences from vectors available in the art, ligating them, and transforming suitable host cells, and to obtain the fusions by expression in the transformed host cells, because Wallach teaches that the fusions it describes are conveniently made by such methods. Finally, it would have been obvious to use the fusion proteins thus produced to inhibit TNF, as in the treatment of diseases including particularly rheumatoid arthritis, because Wallach teaches that the multimers are advantageously employed for such purposes. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

5. Claims 1-3, 6, 8, 15-17, and 19-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallach *et al.*, EP 0 526 905.

The Wallach EP publication is substantially identical to the U.S. patent relied upon in the rejection above. Wallach '905 describes and claims multimers of TNFR moieties, each such moiety corresponding to a soluble TNFR polypeptide, including particularly the extracellular domains of the p55 and p75 human TNFRs (abstract; page 2). It teaches that because both TNF and its receptors function *in vivo* as trimers, the multimeric receptors will be more effective than monomeric soluble receptors in binding to and inhibiting TNF (page 3, lines 3-19). It teaches that dimers or trimers of the TNFR moieties may be advantageously made (claims 2, 3). It teaches that the monomers should be separated by linker moieties of different lengths and that "the optimal linker length will be defined" by routine experimentation (page 7, lines 18-21). It teaches that

either peptide or non-peptide linkers and suitable, and it teaches that the multimers may be conveniently made as contiguous fusion proteins by recombinant methods (Example 4, pages 7-9), incorporating signal sequences as appropriate to the host cell system employed (page 9, lines 22-28). It teaches that the multimers are suitable for the treatment of various TNF-mediated diseases and disorders, including septic shock, cachexia, GVHD, and various autoimmune diseases including rheumatoid arthritis (page 3, lines 29-33). The '905 publication does not exemplify the preparation of any particular fusion multimer, nor does it specify the amino acid sequences of the TNFR monomers or the linker peptides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches that it is advantageous to do so. In the course of making such fusions, it would have been obvious to construct DNA encoding the fusion polypeptide by excising the TNFR sequences from vectors available in the art, ligating them, and transforming suitable host cells, and to obtain the fusions by expression in the transformed host cells, because Wallach teaches that the fusions it describes are conveniently made by such methods. Finally, it would have been obvious to use the fusion proteins thus produced to inhibit TNF, as in the treatment of diseases including particularly rheumatoid arthritis, because Wallach teaches that the multimers are advantageously employed for such purposes. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

6. Claim 14 is objected to as depending from rejected base claims but would be allowable if rewritten in independent form, including all of the limitations of base claim 1 and intervening claim 8.

With reference to the p75 TNFR sequence shown in Fig. 2A of Smith *et al.*, U.S. Patent No. 5,395,760, the claimed DNA encodes a translation product (SEQ ID NO: 2) having the structure $p75_{-22\rightarrow229}$-Arg-$((Gly)_4Ser)_3$-Asp-$p75_{+2\rightarrow234}$. The claimed species falls squarely within the genus of dimeric receptor polypeptides suggested by the prior art. It employs both TNFR and linker structural components corresponding, respectively, to TNF-binding sTNFR and flexible

peptide linker genera also described in the prior art. Moreover, the evidence on this record indicates that the claimed DNA encodes a protein having exactly the functional properties that the prior art teaches that such a fusion is expected to exhibit. Notwithstanding all of this, the references of record do not suggest the single claimed species with the particularity required to support a *prima facie* case of obviousness. *Compare In re Jones,* 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

7. No claim is allowed.

8. This is a continuation of applicant's earlier application serial no. 08/437,533. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action had they been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

*A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED. ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(A) WOULD THEN BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.*

9. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934
Fax	
All formal papers	(703) 308-4242
Informal communications	(703) 308-0294
e-mail (note PTO policies below)	david.fitzgerald@uspto.gov

Inquiries of a general nature should be directed to the Technology Center 1600 receptionists at (703) 308-0196.

DAVID L. FITZGERALD
PRIMARY EXAMINER
ART UNIT 1646

24 March 2000

The best **time to reach Examiner Fitzgerald** is from 9 a.m. to 4 p.m. (Eastern). If he cannot take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the supervisor for this Art Unit, Gary Kunz, may be reached at (703) 308-4623.

Most official papers and all informal **communications may be submitted to the PTO by fax.** For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30. To facilitate their receipt and handling, please —

- Call the examiner when you send an urgent communication.
- **Do not send a duplicate copy** by mail or courier.

Any Internet **e-mail communications will be made of record in the application file**. PTO employees cannot engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. § 122. This policy is more fully set forth in the Interim Internet Usage Policy published in the PTO's *Official Gazette* on 25 February 1997 at 1195 O.G. 89.